quences of ionic binding in the various muscle phases.

Summary. These *in vitro* experiments show that both magnesium and calcium in muscle can contribute to the buffering of pH. In low pH solutions there is a decrease in both calcium and magnesium, and in high pH solutions there is an increase in both calcium and magnesium in muscle.

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Measurement of the Vascular Factor Attending Drug-Altered Sensitivity to Peptic Digestion.* (26400)

ARNOLD S. LEONARD, WARD O. GRIFFEN, JR., DEMETRE M. NICOLOFF, RAYMOND C. DOBERNECK AND OWEN H. WANGENSTEEN

Department of Surgery, University of Minnesota Medical School, Minneapolis

The susceptibility of esophageal, gastric, and duodenal mucosa to acid peptic digestion depends upon pH and pepsin concentration of the gastric juice, the mucous barrier, tissue vascularity, and inherent cellular resistance. Clinical and experimental evidence has shown abetment of the acid peptic ulcer diathesis by various drugs including reserpine(1), serotonin, cortisone(2), pitressin (3) and nitroglycerin(4). It has been shown recently that reserpine increases susceptibility of the esophageal mucosa to acid peptic digestion(5).

The first segment of the experiment concerned assessment of the role of serotonin, ACTH(6) and hydrocortisone(7,8) which are released by reserpine, in the augmented sensitivity of the esophagus to injury by acid peptic juice. Pitressin, nitroglycerin, and chlorpromazine also were evaluated in this respect.

In the second segment of the experiment, the effect of reserpine, chlorpromazine, pitressin, and nitroglycerin on local esophageal blood flow was measured in an attempt to evaluate the importance of the vascular factor in potentiation of acid peptic digestion. A modification of Saperstein's technic was utilized(9).

Method. Adult cats under pentobarbital anesthesia (30 mg/kg) were used. Respiration was maintained by means of an automatic respirator through a cervical tracheostomy. In the first portion of the study, the animals were divided into 7 groups. The technic of perfusion, with different segments of the same cat's esophagus as the control and test preparation was used(5). In Group 5A, however, separate cats were used for control and test preparation. In the latter group, the perfusions using the same patient's gastric juice were started immediately after injecting pitressin intravenously into the test animal. At the end of the procedure, the mucosal surface of the esophagus was inspected. On removal of the esophagus, degree of injury to both segments was graded

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TABLE I. Drug Dosage Schedule and Comparison of Digestion of Control and Test Segments of Esophagus.

Group	No. of cats	Drugs	Dosage	Grade of digestion: Control 0	1	2	3	4	5	Test 0	1	2	3	4	5
I	6	ACTH	25 mg	2	2	2				1	2	3			
II	6	Hydrocortisone	10 "	3	1	2				1	3	2			
III	9	"	50 "	2	3	4				2			2	5	
IV	6	Serotonin	10 "	2	3	1				2	2	2			
V	9	Pitressin	20 units	5	1	2						3	3	3	
V a	12 pr	"	20 " *	2	6	3	1			1	2	1		5	3
VI	8	Nitroglycerin†		6	2					1	1	3		2	1
VII	3	Thorazine	10 mg	1		1	1				1	1		1	
	3	"	25 "	1	1	1				1	1	1			
	3	"	50 "	1	1	1					1	2			

* Perfusions started immediately after cats given pitressin.

† Because of short action, drug given: .65 mg I.M. & I.V. at start of test perfusion and at 60 min. with a .65 mg I.M. at 30 and 90 min.

0 to 5+ (0 : no digestion; 5+ : perforation). All perfusions were done at a pressure of 20 cm and a temperature of 37°C.

In the second segment of the experiment, all cats were prepared with cervical tracheostomy for maintenance of positive pressure respiration, cannulation of the right carotid artery and femoral vein, and exposure of the upper esophagus through a left thoracotomy. The animals were divided into 5 groups according to the intravenous medication: 1) 1 cc sterile H_2O; 2) 0.5 mg reserpine; 3) 25 mg chlorpromazine; 4) 20 u pitressin; 5) 0.65 mg nitroglycerin (intramuscularly and intravenously as in part I).

After a 2 hour period for drug action, arterial blood was taken for hemoglobin determination. Then 60 microcuries of K_{42} was injected rapidly into the femoral vein and simultaneously a continuous flow of blood from the arterial catheter was absorbed on a strip of No. 1 chromatography paper moving at 10 mm/sec. At least 30 seconds after K_{42} injection, a full thickness segment of esophagus was excised and placed in a weighed cuvette. Separate segments of the paper strip representing 2 seconds and the esophageal specimen were counted for gamma activity in a well-counter. The paper segments were analyzed for hemoglobin concentration, and each related to the original hemoglobin value. Number of counts per cc of blood and number of counts per gram esophageal tissue were then calculated. The area beneath the arterial isotope flow curve was determined. Flow in the esophagus was calculated by dividing number of counts per gram by this area, using the principle of the conservation of material (the present method assumes no K_{42} in venous return).

Results. ACTH, serotonin, 10 mg of hydrocortisone and chlorpromazine in doses of 10, 25, and 50 mg produced essentially no change in esophageal sensitivity to peptic perfusion. However, with nitroglycerin and pitressin, and the larger dose of hydrocortisone, marked increased susceptibility to peptic digestion was observed, nitroglycerin producing one perforation and pitressin, 3 perforations. In fact, 75%, 77%, and 66% of the nitroglycerin, single pitressin and paired pitressin-treated esophagi respectively showed greater than 2+ digestion of the drug-treated over the control side (Table I).

Administration of reserpine, pitressin, and nitroglycerin were followed by observed decreases in esophageal blood flow of 63, 35 and 70% respectively. Esophageal blood flow was not changed by chlorpromazine. Cardiac output in reserpine and chlorpromazine groups was similar to the control, whereas pitressin and nitroglycerin produced a 10 and 20% fall in mean cardiac output, respectively.

Discussion. The mechanism of increased susceptibility of esophageal mucosa to acid peptic perfusion induced by reserpine is obscure. A possible explanation is that the endogenous substances released upon reserpine administration are the toxic agents respon-

TABLE II. Esophageal Blood Flow (cc/g/min.).

Group	Control (I)	Reserpine (II)	Chlorpromazine (III)	Pitressin (IV)	Nitroglycerin (V)
No. cats	15	15	11	11	16
Spec. No. 1	1.10	.56	.56	.83	.40
2	.91	.43	5.28	1.45	.25
3	2.93	.28	1.75	1.29	.68
4	2.14	.90	.22	2.02	.69
5	2.19	.72	1.18	.72	.48
6	2.62	.51	1.87	1.38	.43
7	1.00	.48	1.10	1.26	.22
8	1.62	.28	1.65	.77	.55
9	.90	.28	.99	.81	.33
10	1.07	.29	.69	.62	.52
11	1.51	.85	1.25	1.13	.37
12	1.12	1.26			.96
13	1.07	.70			1.31
14	1.76	.80			1.46
15	2.10	.71			.46
16					.24
Mean $\bar{x}$	1.60	.60	1.50	1.12	.58
S.E. $\bar{x}$	.17	.07	.41	.13	.09
P value compared to control		$<<.001$	$>.40$	$>.02$	$<<.001$

sible for lowered tissue resistance. This possibility seems to have been excluded by the present study. A more likely mechanism could be a change of vascular flow resulting in tissue hypoxia, which makes the mucosa vulnerable to digestion. Several previous observations support this contention. Decreased catechol amines in the peripheral vessels, with subsequent increased sensitivity to sympathetic discharge, is known to occur as a reaction to reserpine(10,11). A peripheral vascular alteration has previously been proposed showing potentiation of peptic ulcer formation in cats and dogs given pitressin and nitroglycerin in addition to histamine in beeswax(3,4). Lowered tissue blood flow seems to be the common pathway of enhanced mucosal susceptibility to acid peptic digestion following administration of reserpine, pitressin and nitroglycerin. The possibility of a direct effect of these drugs on cellular metabolism is not excluded; however, the large flow changes observed suggest this as the more likely explanation. Chlorpromazine does not alter local esophageal blood flow nor enhance acid peptic digestion of the esophagus.

Conclusions. Tissue resistance to peptic digestion is decreased significantly by pitressin and nitroglycerin and by large doses of hydrocortisone. Reserpine, pitressin and nitroglycerin produced decreased esophageal blood flow. These experiments suggest definitely that decrease in blood flow abets the ulcer diathesis.

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